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10/538,226	06/06/2005	Marnix L Bosch	020093-004010US	9406

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,226	BOSCH, MARNIX L	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 13-32, species: 1) BCG and interferon gamma, or LPS, TNF-alpha as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule are examined in the instant application.

The species dendritic cells obtained from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood has been rejoined with the species dendritic cells obtained from peripheral blood, the species LPS and TNF-alpha have been rejoined with the species BCG and interferon gamma, and the species CD80 has been rejoined with the species CD86, because these species have been found in the art.

The species: 1) maturation agent, which is an imidazoquinoline compound, a synthetic double stranded polyribonucleotide, a agonist of a Toll-like receptor (TLR), a sequence of nucleic acids containing unmethylated CpG motifs known to induce the maturation of DC, or any combination thereof, and 2) co-stimulatory agent CD54 have been withdrawn from consideration, as being drawn to non-elected species.

Withdrawn Rejection

The 112, first paragraph rejection has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5 remain rejected under 35 U.S.C. 102(b) as being anticipated by Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 10/18/07.

The reponse asserts that Labeur et al fail to teach that the partially matured dendritic cells have not been exposed to tumor. The response asserts that the dendritic cells taught by Labeur et al are contacted with antigen before administration to an individual to be treated.

The response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur et al certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 2-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, supra, in view of Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record in paper of 10/18/07.

The reponse asserts that Labeur et al fail to teach that the partially matured dendritic cells have not been exposed to tumor. The response asserts that the dendritic cells taught by Labeur et al are contacted with antigen before administration to an individual to be treated. The response asserts that Murphy et al may teach various source for dendritic cell precursors, and method for in vitro contacting the dendritic cells with a prostate cancer antigen, but there is no teaching or suggestion for administrating partially matured dendritic cells that have not been exposed to tumor antigen.

The response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught

by Labeur et al certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

2. Claims 6-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), for reasons already of record in paper of 10/18/07.

The reponse asserts that Labeur et al fail to teach that the partially matured dendritic cells have not been exposed to tumor. The response asserts that the dendritic cells taught by Labeur et al are contacted with antigen before administration to an individual to be treated. The response asserts that there is no teaching or suggestion in Bosch et al or Chakraborty et al for administrating partially matured dendritic cells that have not been exposed to tumor antigen.

The response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur et al certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

3. Claims 13-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, for reasons already of record in paper of 10/18/07.

The reponse asserts that Labeur et al fail to teach that the partially matured dendritic cells have not been exposed to tumor. The response asserts that the dendritic cells taught by Labeur et al are contacted with antigen before administration to an individual to be treated. The response asserts that as such it would not have been obvious to choose direct administration of DCs over subcutaneous injection.

The response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur et al certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to replace s.c. injection of the DCs taught by Labeur et al with other common direct method of administration, such as administration of DCs directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, because subcutaneous injection is not the optimal cell delivery system for in vitro generated DCs, at least in the mice, in view that DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur et al.

4. Claims 19-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Labeur et al, 1999, J Immunol, 162: 168-175, supra, in view of Nikitina et al, 2001, Int J Cancer, 94: 825-833, IDS# AN of 05/09/07, for reasons already of record in paper of 10/18/07.

The reponse asserts that Labeur et al fail to teach that the partially matured dendritic cells have not been exposed to tumor. The response asserts that the dendritic cells taught by Labeur et al are contacted with antigen before administration to an individual to be treated. The response asserts that it is not the claimed invention that the DCs taught by Labeur et al are administered to patients that had received radation therapy.

The response has been considered but is not found to be persuasive for the following reason:

The response argues limitation not in the claims. The claims do not limit that the administered, partially matured dendritic cells have not been exposed to tumor and that the ability to take up and process antigen by the dendritic cells is *in vivo*. The dendritic cells taught by Labeur et al certainly can take up and process antigen. Said dendritic cells are able to induce an anti-tumor response subsequent to administration to a cancer patient.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration taught by Labeur et al with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina et al.

5. Claims 21-23, 27-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, IDS# AU of 05/09/07, in view of Sukhatme et al (US 6,797,488), and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claims 6-9 above, and further in view of Sukhatme et al (US 6,797,488), for reasons already of record in paper of 10/18/07.

The response asserts that the DCs taught by Triozzi et al are immature dendritic cells and are not partially matured dendritic cells. The response asserts that Sukhatme et al teach a pharmaceutical composition, and do not teach or suggest the claimed invention.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs taught by Triozzi et al, which are exposed to GM-CSF and IL-4, has the same property as the claimed DCs, i.e. having upregulated CD80, CD86, as taught by Triozzi et al, and exhibits an intermediate maturation stage, as evidenced by Labeur et al. Labeur et al teach that DCs cultured in the presence of GM-CSF only are immature (p.169, first column, first paragraph). Labeur et al teach that DCs cultured in the presence of GM-CSF and IL-4, with or without the addition of Flt3L or TNF-alpha, exhibit an intermediate maturation stage (p.169, first column, second paragraph). An intermediate maturation stage is reasonably interpreted as partially matured. Labeur et al further teach that DCs generated from GM-CSF and IL-4, with or without the addition of TNF-alpha, exhibit intermediate ability to present antigen, after being

exposed to the antigen (p.8, last paragraph, bridging p.9 and figure 3 on page 9), which is the same as the claimed ability to uptake and process antigen.

Although the Triozzi reference does not explicitly teach that the generated DCs are partially mature, and retain the ability to uptake and process antigen, however, the claimed DCs appear to be the same as the prior art DCs, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs taught by Triozzi et al with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for their storage.

The response asserts that DCs taught by Labeur et al are contacted with tumor antigen prior to administration. The response asserts that one would not have expected that non-terminally mature DCs exhibit up-regulated CD80 and CD86. The response asserts that Labeur et al cannot be combined with Bosch et al and Chakraborty et al. The response asserts that the DCs taught by Chakraborty et al are mature DCs.

The response has been considered but is not found to be persuasive for the following reasons:

Concerning the arguments that DCs taught by Labeur et al are contacted with tumor antigen prior to administration, the response argues limitation not in the claims. Further, the DCs taught by the combined art has the same property as the claimed DCs, because: 1) DCs produced by a combination of only GM-CSF and IL-4 produce IL-12, and not IL-10, as taught by Chakraborty et al (table 1 on page 90), 2) up-regulation of CD80 and CD86 are property of DCs that produce IL-12, as taught by Chakraborty et al, and 3) DCs cultured in the presence of GM-CSF and IL-4, with or without the addition of Flt3L or TNF-alpha, exhibit an intermediate maturation stage as taught by Labeur et al (p.169, first column, second paragraph).

6. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, in view of Sukhatme et al (US 6,797,488), and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, as applied for claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record in paper of 10/18/07.

The response asserts that the DCs taught by Triozzi et al are immature dendritic cells and are not partially matured dendritic cells. The response asserts that Sukhatme et al teach a pharmaceutical composition, and do not teach or suggest the claimed invention. The response asserts that Murphy et al teach cryopreservation, and thus do not teach or suggest each element of the claimed composition.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs taught by Triozzi et al, which are exposed to GM-CSF and IL-4, has the same property as the claimed DCs, i.e. having upregulated CD80, CD86, as taught by Triozzi et al, and exhibits an intermediate maturation stage, as evidenced by Labeur et al, supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al, using the method taught by Murphy et al, for extended use of the generated DCs.

The response asserts that Labeur et al do not teach the partially mature DCs of the claimed invention. The response asserts that a combination of Labeur et al, Bosch et al, Chakraborty et al, and Murphy et al fail to teach or suggest each and every element of claim 24.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs taught by the combination of Labeur et al, Bosch et al, Chakraborty et al has the same property as the claimed DCs, supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Labeur et al, Bosch et al and Chakraborty et al, using the method taught by Murphy et al, for extended use of the generated DCs.

7. Claims 25-26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Triozzi et al, 2000, Cancer, 89: 2646-54, in view of Sukhatme et al (US 6,797,488), and as evidenced by Labeur et al, 1999, J Immunol, 162: 168-175, as applied for claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), or **in the alternative**, over Labeur et al, 1999, J Immunol, 162: 168-175, in view of US 20050059151 (Bosch et al, which has as priority US 60/317592, filed on 09/06/01), and Chakraborty et al, 2000, Clin Immunol, 94(2): 88-98, IDS # AF of 05/09/07), as applied to claim 21, and further in view of Murphy et al (US 5,788,963, filed on 07/31/1995), for reasons already of record in paper of 10/18/07.

The response asserts that a combination of Triozzi et al, Sukhatme et al, and Labeur et al, and Murphy et al fail to teach or suggest each and every element of claims 25-26.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs taught by the combination of Triozzi et al, Sukhatme et al, and Labeur et al has the same property as the claimed DCs, supra.

It would have been obvious that the DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al have been isolated from the individual to be treated, as suggested by Murphy et al, to avoid unwanted rejection of foreign DCs. It would have been obvious that the DCs taught by Triozzi et al, Sukhatme et al, and Labeur et al have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because

antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

The response asserts that a combination of Labeur et al, Bosch et al, Chakraborty et al, and Murphy et al fail to teach or suggest each and every element of claims 25-26.

The response has been considered but is not found to be persuasive for the following reasons:

The DCs taught by the combination of Labeur et al, Bosch et al, Chakraborty et al has the same property as the claimed DCs, supra.

It would have been obvious that the DCs taught by Labeur et al, Bosch et al and Chakraborty et al have been isolated from the individual to be treated, as suggested by Murphy et al, to avoid unwanted rejection of foreign DCs. It would have been obvious that the DCs taught by Labeur et al, Bosch et al and Chakraborty et al have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy et al, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy et al. Further, an HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy et al.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time

policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
June 9, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643